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Solvent-free fluorination of organic compounds using N–F reagents

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Abstract—Efficient fluorination of 1,3-dicarbonyl compounds, enol acetates of aromatic ketones, and activated aromatic compounds was achieved under solvent-free conditions using Selectfluor™ F–TEDA–BF_4 or Accufluor™ NFSi.

1. Introduction

Interest in fluorine-containing organic molecules has been increasing since this element very often induces beneficial changes in their specific physicochemical and biological characteristics.[1,2] The main problem in performing selective and efficient fluorination of organic compounds is connected with the low dissociation energy of the fluorine–fluorine bond and the strength of the fluorine–carbon bond. The solution to this problem is focused on the development of special methodologies for modulation of the extreme reactivity of molecular fluorine (low temperature techniques[3] and high dilution with an inert gas,[4] using strong acids as reaction media[5] or, more recently, micro-reactor technology[6]), or in the design of F–L type reagents, where 'L' represents the ligand part of the fluorinating reagent. This second concept has resulted in the development of a variety of fluorinating reagents known under the common name 'electrophilic fluorinating reagents', consisting of three main classes: fluoroxy compounds,[7] xenon fluorides,[8] and N–F reagents.[9–11]

In line with the concept and principles of green chemistry which emerged a decade ago,[12] the suitability of safer alternative reaction media in place of volatile or toxic organic solvents is one of the major and still challenging issues. Accepting this challenge in the field of organofluorine chemistry, we have already shown that selective and efficient fluorination of a variety of organic compounds could be performed in aqueous media using F–TEDA–BF_4,[13] however, in the scope of green chemistry, the best solvent is regarded as 'no solvent at all'.[14] Fluorofunctionalization of organic compounds under these conditions is a rather unexplored area. Research has been mainly focused on solvent-free nucleophilic fluorination, such as nucleophilic aromatic substitution with KF in the presence of a phase transfer catalyst,[15] regioselective and stereoselective opening of epoxides by $NBu_4H_2F_3$,[16] or using electrochemical techniques for fluorination of cyclic ethers and lactones.[17] To our knowledge it is still not clear whether solvent-free fluorination using electrophilic fluorination reagents could be efficiently and selectively performed, although Differding briefly noted fifteen years ago that neat anisole (in 22-fold molar excess at 150 °C) and acetanilide (in two-fold molar excess at 100 °C) were fluorinated using NFSi.[18] We now report our recent efforts in responding to the challenging question of whether it is possible to selectively and efficiently transform a C–H bond to a C–F bond with electrophilic fluorinating reagents under solvent-free conditions.

In the case of solvent-free reactions the aggregate state of the substrates and reagents plays an important role in molecular migration and thus has a significant influence on the transformation. Improved contact between the reagent and substrate can be established in the case of liquid–liquid and liquid–solid systems. We decided to start our investigation with liquid β-keto esters and selected representatives of each class of N–F reagents, all solids. In a typical experiment a mixture of 1 mmol of β-keto ester **2** or **4** and 1.1 mmol of N–F reagent **1** was heated in a 15 ml reaction flask at 85 °C for 4 h and the crude reaction mixture obtained analysed. As

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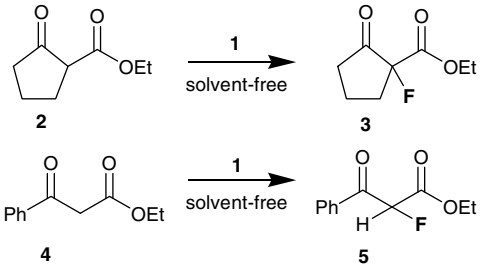
Table 1. Fluorination of β-ketoesters with N–F reagents **1**[a] under solvent-free conditions



Entry	Substrate	N–F (**1**)	Time (h)	Yield[b] (%)
1		**a**: NFTh	4	Trace
2		**b**: FB-P300	4	Trace
3	**2**	**c**: F–TEDA–BF_4	6	71 (76)
4		**d**: NFSi	1	89 (82)
5		**a**: NFTh	4	Trace
6	**4**	**b**: FB-P300	5	Trace
7		**c**: F–TEDA–BF_4	5	82[c] (76)
8		**d**: NFSi	5	87[c] (81)

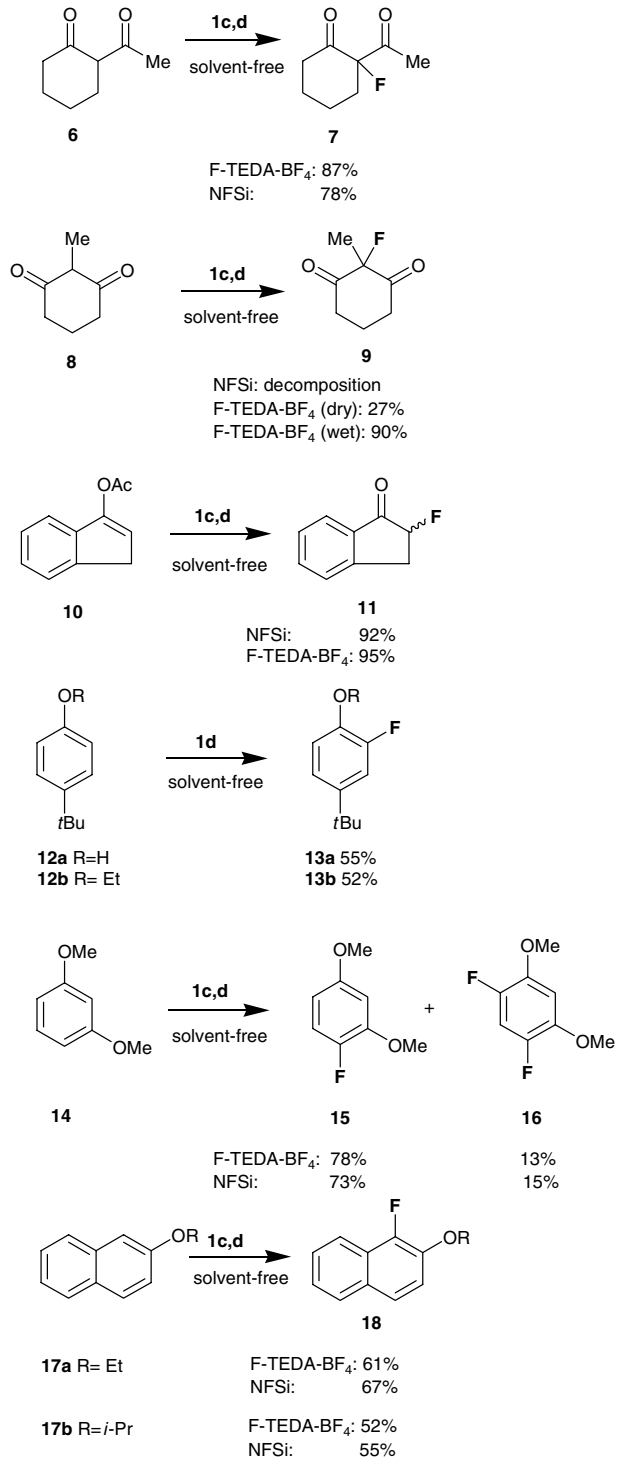
[a] Compounds **1a**: Accufluor™ NFTh:[11] 1-fluoro-4-hydroxy-1,4-diazoniabicyclo [2.2.2]octane bis(tetrafluoroborate); **1b**: FB-B3009: *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate; **1c**: Selectfluor™ F–TEDA–BF_4:[11] 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]-octane bis(tetrafluoroborate); **1d**: Accufluor™ NFSi: *N*-fluorobenzensulfonimide.[9]

[b] Values in brackets are yields of pure products isolated by column chromatography (SiO_2; CH_2Cl_2–*n*-hexane = 1:9).

[c] 8–10% of 2,2-difluoro-3-oxo-3-phenylpropionic acid ethyl ester was also formed.[19]

shown in the Table 1, both ethyl 2-oxocyclopentanecarboxylate **2** and 3-oxo-3-phenylpropionic acid ethyl ester **4** were efficiently transformed under solvent-free conditions to their corresponding fluoro derivatives, that is, ethyl 1-fluoro-2-oxocyclopentanecarboxylate **3** and 2-fluoro-3-oxo-3-phenylpropionic acid ethyl ester **5**, using Selectfluor™ F–TEDA–BF_4 **1c** (entries 3 and 7) or Accufluor™ NFSi **1d** (entries 4 and 8), while application of Accufluor™ NFTh **1a** (entries 1 and 5) or FP-B300 **1b** (entries 2 and 6) were unsuccessful leading to only trace amounts of the corresponding fluorinated products **3** or **5** in these cases.

Encouraged by these results we further investigated the possibility of fluorination of 1,3-diketones under solvent-free conditions and chose derivatives structurally similar to the mentioned targets: that is, 2-acetylcyclohexanone **6**, which is a liquid, and solid 2-methyl-1,3-cyclohexadione **8**. We established that **6** was readily converted after 4 h to 2-fluoro-2-acetylcyclohexanone **7** in 78% yield with 1.1 mmol of NFSi at 85 °C, while an even more efficient transformation (87%) was obtained using F–TEDA–BF_4 (Scheme 1). On the other hand, the treatment of **8** with dry NFSi at 85 °C caused a vigorous and uncontrollable reaction, resulting in decomposition of the materials, while F–TEDA–BF_4 under the same conditions gave the expected 2-fluoro-2-methyl-cyclohexadione **9**, but in only 27% yield. The addition of a drop of water (25–30 mg) to a mixture of F–TEDA–BF_4 and **8** prior to heating considerably improved the efficiency of the transformation and excellent conversion



Scheme 1.

to **9** was established. 1-Indanone, as a monocarbonyl substrate, could not be directly fluorinated under solvent-free conditions, but after its transformation to acetyl-3*H*-indene **10** an almost quantitative conversion to 2-fluoro-1-indanone **11** was achieved with both the N–F reagents employed.

In order to check the possibility of formation of a C–F bond under solvent-free conditions in aromatic compounds, we chose 4-*tert*-butyl-phenol **12a** as a model

compound and established that by heating it at 85 °C for 4 hours with 1.1 mmol of NFSi, 2-fluoro-4-*tert*-butylphenol **13a** was formed in 55% of yield accompanied with trace amounts of 4-fluorophenol and 2,6-difluoro-4-*tert*-butyl phenol. Similar results were observed when 1-*tert*-butyl-4-ethoxybenzene **12b** was treated under the same reaction conditions to afford 1-*tert*-butyl-4-ethoxy-2-fluorobenzene **13b** as the main product, accompanied by a trace amount of 1-ethoxy-4-fluorobenzene. The use of F–TEDA–BF_4 in these two cases did not lead to formation of any product. On the other hand, F–TEDA–BF_4 was found to be efficient in the case of 1,3-dimethoxybenzene **14** which was readily converted into 4-fluoro-1,3-dimethoxybenzene **15** as the major product, and 4,6-difluoro-1,3-dimethoxybenzene **16**, as the minor product, with a high overall yield. The same mixture of products was also established when NFSi was used under the same reaction conditions. Electrophilic fluorination under solvent-free conditions was also efficient in the case of 2-alkoxynaphthalene derivatives. 2-Ethoxy-**17a** and 2-isopropyloxynaphthalene **17b** were converted with both N–F reagents at 85 °C into 1-fluoro-alkoxynaphthalene derivatives **18** in reasonable yield, while only trace amounts of 1,1-difluoro-2(1*H*)-naphthalenone, the consequence of further fluorination, were detected (Scheme 1).

In conclusion direct selective fluorination under solvent-free conditions was successfully achieved using electrophilic fluorinating reagents from the N–F class. The best results were obtained by heating the organic compound, liquid or solid, with F–TEDA–BF_4 or NFSi, at 80–90 °C. Solvent-free fluorination was efficiently and selectively achieved on a variety of β-diketones, β-keto esters, acetylated mono ketones, and various activated aromatic derivatives. Following our preliminary findings it has thus been shown that transformation of a carbon–hydrogen bond into a carbon–fluorine bond could also be selectively and efficiently achieved under solvent-free conditions.

2. Typical experimental procedure for solvent-free fluorination of organic compounds with N–F reagents

In the case of liquid substrates 1 mmol of target material and 1.1 mmol of N–F reagent were homogenized in a 15 ml glass vessel using a glass stick and the mixture heated at 85–90 °C for 1–8 h, while in the case of solid target compounds the mixture of substrate and N–F reagent was triturated in a glass mortar for a minute, then transferred to a glass vessel and heated. After routine work-up procedures for NFSi[9a] or F–TEDA–BF_4,[20] the crude reaction mixtures were analyzed by ^{19}F and ^{1}H NMR spectroscopy using octafluoronaphthalene as an internal standard.[21] Pure products were isolated by column chromatography.

References and notes

1. (a) *Organo-Fluorine Compounds Houben-Weyl Methods of Organic Chemistry*; Baasner, B., Hagemann, H., Tatlow, J. C., Eds.; Georg Thieme: Stuttgart, New York, 1999; Vol. E10a–c; (b) Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell: Oxford, 2004.
2. (a) *Organofluorine Chemistry. Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum Press: New York, London, 1996; (b) *Advances in Organic Synthesis Modern Organofluorine Chemistry—Synthetic Aspects*; Laali, K. K., Atta-Ur-Rahman, Eds.; Bentham Science: Amsterdam, 2006; Vol. 2.
3. Merrit, R. F.; Johnson, F. A. *J. Org. Chem.* **1966**, *31*, 1859–1863.
4. (a) Purrington, S. T.; Kagen, B. S.; Patrick, T. B. *Chem. Rev.* **1986**, *86*, 997–1018; (b) Rozen, S. *Acc. Chem. Rev.* **1988**, *21*, 307–312; (c) Chambers, R. D.; Parsons, M.; Sandford, G.; Thomas, E.; Trmcic, J.; Moilliet, J. S. *Tetrahedron* **2006**, *62*, 7162–7167, and references cited therein.
5. (a) Chambers, R. D.; Skinner, C. J.; Thomson, J.; Hutchinson, J. C. S. *Chem. Commun.* **1995**, *17*; (b) Chambers, R. D.; Holling, D.; Sanford, G.; Batsanov, A. S.; Howard, J. A. K. *J. Fluorine Chem.* **2004**, *125*, 661–671, and references cited therein.
6. (a) Chambers, R. D.; Spink, R. C. H. *Chem. Commun.* **1999**, 883–884; (b) Chambers, R. D.; Fox, M. A.; Sanford, G. *Lab Chip* **2005**, *5*, 1132–1139, and references cited therein.
7. Rozen, S. *Chem. Rev.* **1996**, *96*, 1717–1736.
8. (a) Zupan, M. In *The Chemistry of Functional Groups, supplement D2, The Chemistry of Halides, Pseudo-Halides and Azides*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1995; pp 821–860; (b) Zajc, B. in Ref. 2b, 61–157.
9. (a) Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737–1755; (b) Taylor, D. S.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431–12477.
10. Umemoto, T. in Ref. 2b, pp 159–181 and references cited therein.
11. (a) Singh, R. P.; Schreeve, J. M. *Chem. Res.* **2004**, *37*, 31–34; (b) Stavber, S.; Zupan, M. in Ref. 2b, pp 213–268 and references cited therein.
12. Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998.
13. Stavber, G.; Zupan, M.; Jereb, M.; Stavber, S. *Org. Lett.* **2004**, *6*, 4973–4976.
14. (a) *Solvent-free Organic Synthesis*; Tanaka, K., Ed.; Wiley: Weinheim, 2003; (b) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025–1074; (c) Prakash, G. K. S.; Mathew, T.; Hoole, D.; Esteves, P. M.; Wang, Q.; Rasul, G.; Olah, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 15770–15776, and references cited therein; (d) Pravst, I.; Zupan, M.; Stavber, S. *Green Chem.* **2006**, *8*, 1001–1005, and references cited therein.
15. Marque, S.; Snoussi, H.; Loupy, A.; Plé, N.; Turck, A. *J. Fluorine Chem.* **2004**, *125*, 1847–1851.
16. Barbier, P.; Mohr, P.; Muller, M.; Masciadri, R. *J. Org. Chem.* **2002**, *63*, 6984–6989.
17. Hasegava, M.; Ishii, H.; Fuchigami, T. *Tetrahedron Lett.* **2002**, *43*, 1503–1505.
18. Differding, E.; Ofner, H. *Synlett* **1991**, 187–189.
19. The use of two molar excess of the N–F reagents **1c**,**d**, contrary to the reaction in water,[13] did not considerably improve the formation of the 2,2-difluoro product, while fluorination of mono fluoro compound **5** with an equimolar amount of the N–F reagent afforded no more than 15% of the difluoro product.
20. Zupan, M.; Iskra, J.; Stavber, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1655–1660.
21. A gram scale experiment was performed in the case of fluorination of compound **8** with **1c** and no uncontrollable exotherm was observed.